REMARKS

The Office Action dated August 22, 2008 has been carefully considered and the following response prepared. Claims 3-7, 9, 10, 16, 18, 19, 21, 25, and 26 are pending in the application. Claim 16 has been amended. Support for the amendment to claim 16 can be found throughout the specification and in particular at page 7, lines 19 and 20.

New claims 27-33 have been added. New claims 27-29 are directed to formulations and depend from claim 16. Support for new claims 27-29 can be found throughout the specification and in particular at page 7, lines 15-20 and page 10, lines 12-19 and 26-27. New claims 30-33 are directed to methods for averting or reducing the risk of postoperative ischemia-reperfusion injury and depend from claim 10. Support for new claims 30-33 can be found throughout the specification and in particular at page 5, lines 11-15, and page 10, lines 12-19 and 26-27.

REJECTION UNDER 35 USC 102(b)

At page 3 of the Office Action, the Examiner rejected claims 16, 18-19 and 26 under 35 USC 102(b) as anticipated by Kogirima et al. (JP 2001139481). The Examiner alleged that Kogirima et al. discloses a composition which comprises green tea extract and glutamine.

Applicants traverse this rejection. Claim 16 has been amended to recite that component b), at least one NO donor or precursor thereof, is present in the composition in the amount of 0.1 – 150 grams/1,000 ml of the formulation. Claims 18-19 and 26 depend from claim 16, and are also amended by the amendment to claim 16.

Kogirima et al. discloses a green tea extract that contains 0.9 micrograms/ml of glutamine. This amount is far less than the amount of glutamine in the formulation of amended claim 16, which contains 0.1 – 150 grams/1,000 ml of the formulation of at least one NO donor which is a substrate of NO synthetase, or a precursor of this NO donor, wherein the NO donor and precursor are selected from the group consisting of glutamine, and precursors of glutamine in the form of a di- or tripeptide containing glutamine, or the physiologically tolerated salts or combinations thereof.

Claims 16, 18-19 and 26 are not anticipated Kogirima et al. Withdrawal of this section 102(b) rejection is respectfully requested.

REJECTION UNDER 35 USC 103

At pages 3-10 of the Office Action, the Examiner rejected claims 3-10, 16, 18-19 and 21-25 under 35 USC 103 as unpatentable over Zhong et al. Am. J. Physiol Gastrointest Liver Physiol 283: G957-G964 (2002), Schneider et al. (U.S. Patent 6,656,608), Sherrat et al. (U.S. Patent 6,423,349), Schneider et al (U.S. Patent 5,902,829) and Yokozowa et al. Exp Toxicol Pathol 49(5): 329-335 (2002).

The Examiner alleged that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the green tea extract taught by Zhong et al., and the glycine and glutamine taught by Schneider et al. '608 patent, Sherratt et al. and Schneider '829 patent, respectively, to obtain a composition which would be useful for treating preoperative patients to reduce the risk of ischemia reperfusion. The Examiner further alleged that the administration time taught by the instantly cited references would render obvious the instantly claimed administration which takes place less than twenty-four hours before surgery because the references teach administration which begins before surgery, and administration that begins any time prior to surgery and continues until the surgery would be taking place less than twenty-four hours prior to surgery, as instantly claimed. The Examiner considered the adjustment of particular conventional working conditions, i.e. timing of administration of the composition before or after surgery, to be merely a matter of judicious selection and routine optimization which is well within the skill in the art.

Applicants traverse this rejection.

Zhong et al., discloses the use of green tea extract to reduce hepatic ischemia-reperfusion injury in rats. Rats were fed green tea extracts starting five days prior to surgery, and were fasted overnight before surgery with hepatic warm ischemia and reperfusion.

Schneider et al. (U.S. Patent 5,656,608) disclose the use of one or more of the amino acids glycine, alanine and serine in combination with a) omega-3 polyunsaturated fatty acids; b)

arginine or ornithine or pharmaceutically acceptable salt of arginine or ornithine; or c) RNA, nucleotide or nucleoside; or mixtures of one or more of a), b) and c) to prevent or minimize the effects of hypoxia-reperfusion injury. When used to minimize the effects of ischemia-reperfusion injury, column 7, lines 9-13 disclose that a dietary supplement containing the foregoing can be administered over a period of three days or longer before surgery, generally three to six days before surgery. Such supplements are disclosed at column 6, lines 21-61 as comprised of energy sources in an amount supplying from 600 to 1,000 Kcal/day. Schneider et al. does not disclose or suggest administration of green tea extract for any purpose, much less to prevent or reduce postoperative complications.

Sherratt et al. discloses compositions comprising glutamine in combination with other nutrients, including N-acetyl-cysteine and Vitamins A, C, and E, that can be administered for promoting recovery in patients undergoing elective surgery, and for treating multiple organ system failure. The compositions are administered to patients before and after elective surgical procedures, in particular 1-2 days prior to and/or after elective surgical procedures

Schneider ('829 patent) discloses the use of L-arginine, a precursor of L-arginine and/or physiologically acceptable salts thereof, or (i) a nitric oxide donor, and/or (ii) a substrate of the nitric oxide synthetase, and/or (iii) a precursor of the said substrate, in the preparation of a medicament or nutritional formulation for the amelioration of microcirculatory hypoperfusion, and/or the treatment or prophylaxis of hypoperfusion-reperfusion injury, in patients which have undergone elective surgery, characterized in that the medicament or nutritional formulation is pre-operatively administered to the patient. Schneider et al. ('829 patent) discloses glutamine as a precursor of L-arginine. Schneider et al. ('829 patent) further discloses that the medicament is administered at least one day prior to surgery, but can be initiated between 3-10 days prior to surgery.

Yokozawa et al. discloses experiments on the influence of green tea and its three major components upon low-density lipoprotein oxidation.

None of the cited references, alone or in any combination, disclose or suggest the claimed methods of averting or reducing the risk of postoperative complications wherein a composition

comprising a) green tea extract and b) at least one NO donor which is a substrate of NO synthetase, or a precursor of this NO donor, wherein the NO donor and precursor are selected from the group consisting of glutamine, and precursors of glutamine in the form of a di- or tripeptide containing glutamine, or the physiologically tolerated salts or combinations thereof, is gastrointestinally administered to a surgical patient, wherein administration of the composition takes place less than twenty-four hours before a surgical procedure. There is no disclosure or suggestion in any of the references of administration of a composition comprising a) green tea extract and b) at least one precursor of glutamine in the form of a di- or tripeptide containing glutamine, or the physiologically tolerated salts thereof, or combinations thereof, for averting or reducing the risk of postoperative complications, as claimed in new claim 33, or the formulation of new claim 27. Moreover, there is no disclosure or suggestion of administering to a surgical patient a composition comprising a) green tea extract and b) at least one NO donor which is a substrate of NO synthetase, or a precursor of this NO donor, less than twelve hours, less than six hours or less than three hours before a surgical procedure, as claimed in new claims 30-32.

There is no suggestion or motivation to modify the cited references by adjusting the time of administration such that the composition comprising green tea extract and at least one NO donor or precursor thereof is administered less than 24 hours before a surgical procedure. The periods of administration of Zhong et al., the Schneider '608 patent, Sherratt et al., and the Schneider '829 patent, whether before surgery or after, are much longer than the periods recited in claims 10 and 25, and new claims 30-32.

Persons skilled in the art looking to administer a composition containing the green tea extract from Zhong et al., glutamine from Sherratt et al. or the Schneider '829 patent and glycine from the Schneider et al. '608 patent would be more likely to adjust the time of administration of such a composition to a longer time period before surgery than a shorter period of less than 24 hours as recited in the claimed methods. Zhong et al. administered green tea extract for a period of five days before surgery. The Schneider et al. '608 patent suggests administering the dietary supplement for three days or longer before surgery, generally three to six days before surgery. In Sherratt et al. the compositions are administered to patients 1-2 days prior to and/or after elective surgical procedures. The Schneider et al. '829 patent discloses that the medicament is

administered at least one day prior to surgery, but can be initiated between 3-10 days prior to surgery.

Based on the disclosures of the cited references, the skilled person would thus most likely select a starting time for administration of the composition near the five days prior to surgery disclosed in Zhong et al. to have a better chance of obtaining a reduction in ischemia/reperfusion injury from a composition containing green tea extract and glutamine, or green tea extract, glutamine and glycine. There was no reasonable expectation of success for adjusting the time of administration of such a composition to a period less than twenty-four hours prior to a surgical procedure. The time periods prior to surgery shown in the cited prior art are days longer than the period recited in the claimed methods, and there is no disclosure or suggestion in any of the cited references that a time period less than twenty-four hour prior to surgery would be effective.

The timing of administration of the composition recited in the claims of the present application is therefore not merely a matter of routine optimization. As discussed in the specification at pages 1-2, what is common to all of the treatments for reducing ischemia-reperfusion injury, cited in the present rejection and/or discussed in the specification, is that they must be performed for at least one day, ordinarily a plurality of days, before a surgical procedure. For patients with an acute need for surgery on an emergency basis, the time available is frequently insuffiicent to achieve a satisfactory result with known methods. The claimed methods and formulation overcome this drawback of known methods. Applicants discovered, contrary to the combined teachings of the cited references that administration of a composition comprising a) green tea extract and b) at least one NO donor or precursor thereof, wherein the NO donor and precursor are selected from the group consisting of glutamine, and precursors of glutamine in the form of a di- or tripeptide containing glutamine, or the physiologically tolerated salts or combinations thereof, less than twenty-four hours before a surgical procedure averts or reduces the risk of postoperative complications. The claimed methods and formulations are especially useful for the support of emergency patients, and other patients in which only a short period, such as a few hours, is available before a surgical procedure.

Claims 3-7, 9, 10, 16, 18-19, 21, and 25, and new claims 27-33 are not obvious in view of the combined teachings of Zhong et al., the Schneider et al. '608 patent, Sherrat et al., the

Schneider et al. '829 patent and Yokozowa. Withdrawal of this section 103 rejection is respectfully requested.

In view of the above, the present application is believed to be in a condition ready for allowance. Reconsideration of the application is respectfully requested and an early Notice of Allowance is earnestly solicited.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 03-2775, under Order No. 09600-00031-US from which the undersigned is authorized to draw.

Dated: November 24, 2008

Respectfully submitted,

By Liza D. Hohenschutz

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